

# *Seresto Evaluation - EPA Meeting*

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23 Mar 2021



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# ATTENDEES

## EPA

### **Edward Messina**

Acting Director, Office of Pesticide Programs

### **Michael Goodis**

Acting Deputy Director, Office of Pesticide Programs

### **Marietta Echeverria**

Acting Director, Registration Division

### **Catherine Aubee**

Associate Director, Registration Division

### **Jennifer Saunders**

Branch Chief, IVB1

### **Jacquelyn Herrick**

Product Manager, IVB1

### **Jamey Shuler**

Risk Manager, IVB1

### **Dana Vogel**

Director, Health Effects Division

### **David Miller**

Branch Chief, Chemistry and Exposure

### **Aaron Niman**

Chemistry and Exposure

### **Shana Recore**

Chemistry and Exposure

### **Elissa Reeves**

Acting Director, Pesticide Reevaluation Division

### **Cathryn Britton**

Branch Chief, RMIB V

### **Melanie Biscoe**

Senior Regulatory Advisor, RMIB V

## ELANCO

### **Sabine Bongaerts**

Vice President Regulatory Affairs and Pharmacovigilance

### **Niels Krebsfaenger**

Executive Director Global Pharmacovigilance

### **Jennifer Schofield**

Principal Scientist Regulatory Affairs

### **Will Heeb**

Director Pharmacovigilance North America

## SCI / PPH / U of M

### **Rick Kingston, Pharm D**

President, Regulatory and Scientific Affairs/Sr. Clinical Toxicologist

### **Ahna Brutlag, DVM, MS, DABT, DABVT**

Director, Veterinary Services & Senior Veterinary Toxicologist



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# SERESTO COLLAR

- There are a number of peer-reviewed articles published in scientific journals regarding the ability of Seresto to prevent transmission of infectious agents
- 2012 RMSF Rodeo (CDC Program)
  - Seresto implemented singularly and in a multi-factorial approach by the Centers for Disease Control (CDC) to decrease tick infestations in a community with a high human fatality rate from RMSF
  - *Drexler N, Miller M, Gerding J, Todd S, Adams L, et al. (2014) Community-Based Control of the Brown Dog Tick in a Region with High Rates of Rocky Mountain Spotted Fever, 2012–2013. PLoS ONE 9(12): e112368. doi:10.1371/journal.pone. 0112368*

## EPA approved label

- Kills and repels fleas and ticks, the vectors of:
  - Lyme Disease
  - Anaplasmosis
  - Rocky Mountain Spotted Fever (RMSF)
  - Ehrlichiosis
  - Bartonellosis
  - Babesiosis
  - Canine Hemoplasmosis
  - Rickettsiosis
  - Cytauxzoonosis
  - Feline Infectious Anemia (Mycoplasma spp.)
  - Tapeworms
- Kills chewing lice
- Aids in treatment of sarcoptic mange



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# INCREASED RECOGNITION OF THE IMPORTANCE OF PREVENTION OF TICK BITES

VOLUME 14 NUMBER 4  
2001

## Commentary

### Prevention of Tick-Borne Diseases: The Need for a Revised Strategy

PETER W. LEE, MD, and CHARLIS NYMAN, MD

**T**icks are important vectors of human infections. In Europe, tick-borne viral encephalitis has been known for several decades, and control measures against the virus have been successful. In the United States, a major problem is Lyme disease, which is a major public health problem. The incidence of Lyme disease in the United States is increasing, and the consequences of the disease are not yet fully understood. In the United States, the consequences of the disease are not yet fully understood. In the United States, the consequences of the disease are not yet fully understood.

More tick-borne infections are now being recognized. Tick-borne diseases and infections are significant problems, and treatment and prevention are also being recognized. Tick-borne diseases and infections are significant problems, and treatment and prevention are also being recognized.

About Medical Writing

*"The important thing is, however, that we have to put much more research emphasis than before on how to repel ticks. This would be simpler and cheaper than vaccination or antibiotics, not to speak of the treatments for tick-borne diseases."*

Wahlberg P, Nyman D (2001). Prevention of Tick-Borne Diseases: The Need for a Revised Strategy. Vector Borne and Zoonotic Disease 1(4):251-252



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Centers for Disease Control and Prevention  
CDC 24/7: Saving Lives, Protecting People™

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## Ticks

CDC > Ticks Home



### Ticks Home

#### Avoiding ticks

On people

On pets

In the yard

Removing a tick

## Avoiding Ticks

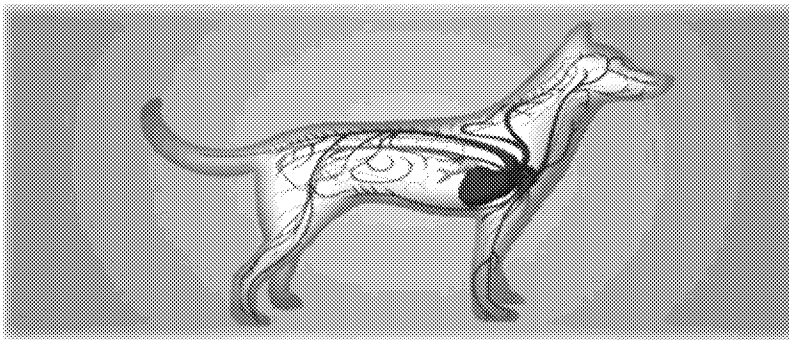
Preventing tick bites

Preventing ticks on your pets

Preventing ticks in the yard

<https://www.cdc.gov/ticks/avoid/index.html>

# SYSTEMIC VS TOPICAL-ACTING PRODUCTS

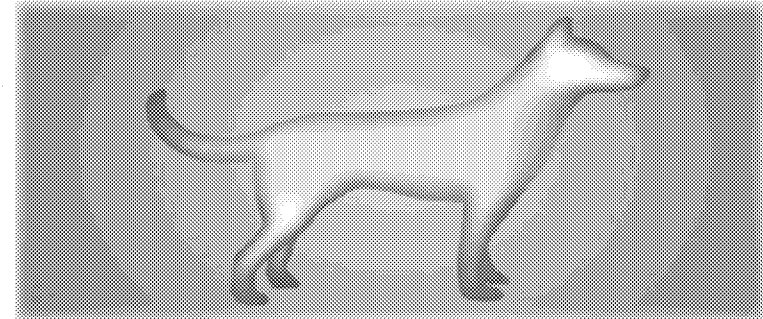


## Systemic Products (FDA)

- Ingested or penetrate the skin
- Tick needs to suck blood containing the active ingredient
- Time between tick attachment and death can put animal at risk

## Topical-Acting Products (EPA)

- Spreads on the skin in thin layer
- Stays topical and works through contact
- Reduces risk of tick-borne diseases by preventing bites and killing quickly



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# Reporting

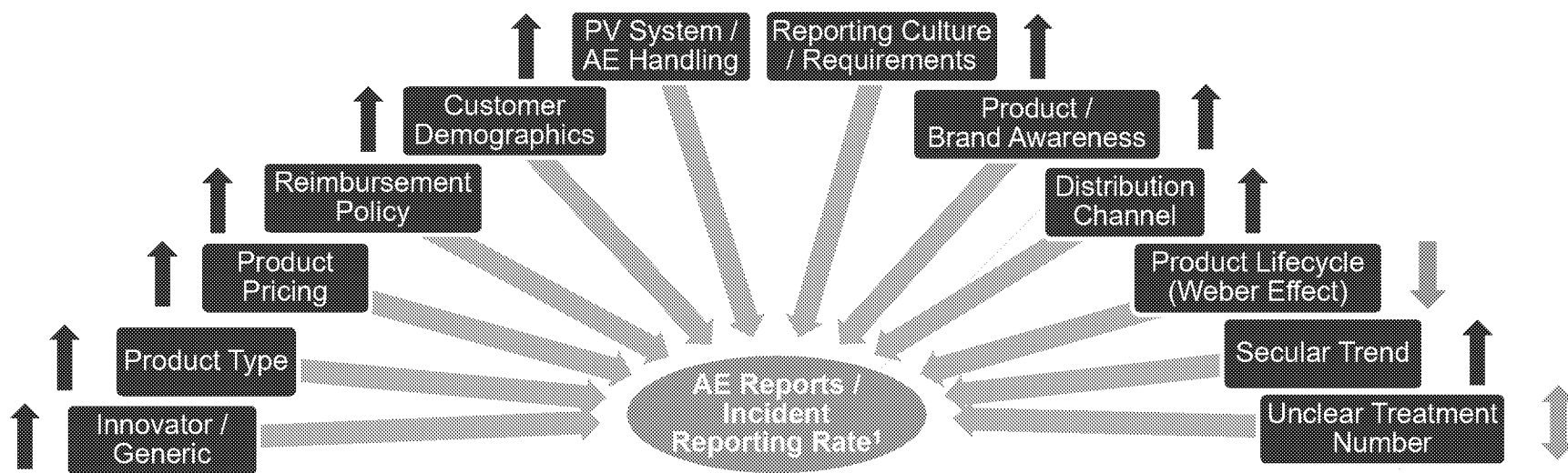
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# REPORTING BIAS

## Independent of product safety profile

PR Notice 98-3 "It should be noted that staff members in EPA's Office of Pesticide Programs (OPP) have many years of experience processing and analyzing incident data, and are well aware of the vagaries of incident reports, such as the frequent lack of specific details, uncertainties of causality, the sometimes erroneous assumptions of reporters, etc. The Agency is also aware that large numbers of incident reports may simply reflect a large product sales volume or the existence of toll-free 800 numbers on product labels, making incident reporting easier."



- These impact factors are NOT related to product safety
- Several of these factors would lead to a higher reporting rate for Seresto in the US – independent of the actual safety profile

Selected examples from diverse sources, e.g.: Amery, 1999, pp. 147-150; Bortnichak and Dai, 1999, pp. 457-461; Hodge, 2009, pp. 262-264;

¹Incident Reporting Rate (the number of incident reports received based on sold treatments in the same period) as opposed to the Incidence Rate (the number of cases occurring in the real world based on treated animals – which is unknown).



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# Ex. 4 CBI



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# Pet Death Reports

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# CAUSALITY ASSESSMENTS

## ABON Coding

A = Probable

B = Possible

O = Unclassifiable / Unassessable

N = Unlikely

NA = No Assessment\*

\* Nullified cases or those involving confirmed counterfeit product

## 2013 – 2020 D-A Reports

ABON Code	Number of Reports
A	5
B	7
O	455
N	1187
NA	198

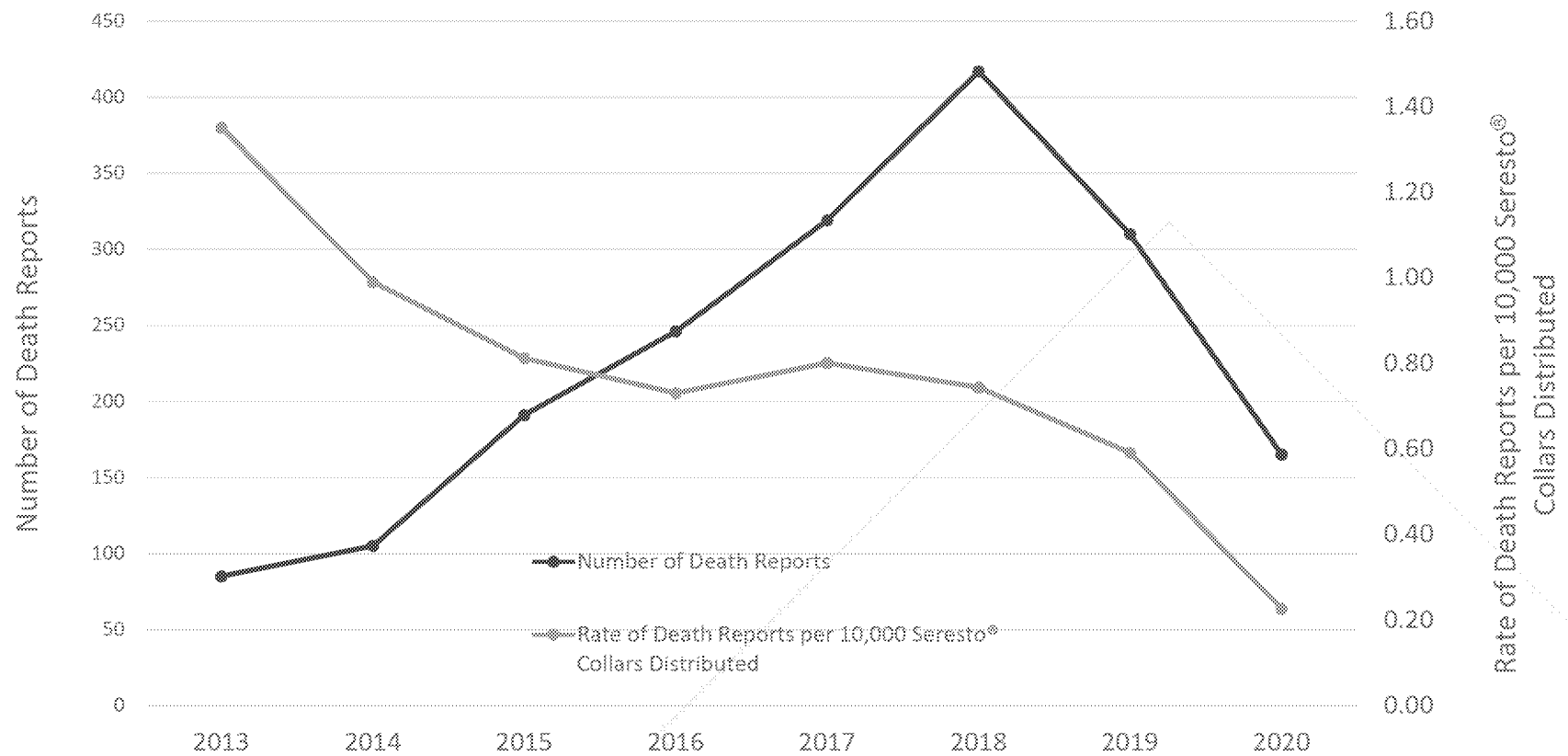
There is no established link between death and exposure to the active ingredients contained in Seresto.



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# DEATH REPORT NUMBERS **AND** REPORTING RATE DECLINING

(all reported deaths without consideration to causality)



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# FURTHER ANALYSIS OF REPORTED DEATH CASES (2012 – 2015)

## 305 dog and 100 cat reports

57% - other causes for death/euthanasia were confirmed / reasonably assumed

- underlying condition, neoplasm, accident, etc.

42% no specific cause to explain the death or euthanasia

- 45% of the pets were 10 years or older
- 63% of these animals were 13 years or older
- 23% were inquiries unrelated to the death of the animal

The clinical signs reported with death are highly variable and heterogeneous. If the effect would be product related, the signs would be expected to focus on one or very few clinical phenomena.

Various estimates exist for the US dog and cat population

- Similar estimates exist for the annual rate of death / euthanasia (millions of animals)
- Contributes to the potential for background noise being reported following the use of Seresto



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# Neurologic

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# NEUROLOGIC

- All reports without consideration to causality
- The reporting rates for PTs from the Neurologic SOC are decreasing over time

Number of reports per 10,000 Seresto® collars distributed by year for the five most frequently reported Neurologic disorder VeDDRA Preferred Terms				
Preferred Term	2017	2018	2019	2020
Ataxia	0.63	0.52	0.54	0.41
Convulsion	0.71	0.42	0.56	0.32
Muscle tremor	0.35	0.29	0.28	0.22
Disorientation	0.12	0.06	0.03	0.05
Central nervous system disorder NOS	0.08	0.05	0.06	0.05



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# NEUROLOGIC / CONVULSIONS

- “Neurological disorders and in particular seizures/epilepsy are very common in pets, mainly in dogs including those not treated with pesticide.” (**Koestner, 1989**)
- “Seizures/epilepsy may have various causes such as heart disorder (e.g. syncope), developmental disorder, metabolic disorder, infection, intoxication, idiopathic epilepsy, trauma, and neoplasia.” (**Koestner, 1989**)
- The prevalence of epilepsy in the normal dog population is described as being between 0.5% and 2%. (**Patterson et al, 2003; Koestner, 1989**)
- Other data describe the incidence rates as 18 cases per 10,000 dog years, which means 18 out of 10,000 dogs (i.e. 0.18%) monitored for a year are expected to show epilepsy. (**Potschka H, 2016**)



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# NEUROLOGIC / CONVULSIONS

Reports of specific neurological adverse effects of a serious and/or idiosyncratic nature in dogs are “very rare.” Factors contributing to the positive safety profile include:

- “Background noise” and “reporting bias”:
  - Background prevalence of seizures/convulsions in dogs (~0.5-2%)
  - Long use of product (duration of up to 8 months) results in an increased likelihood of convulsions or idiopathic epileptic event occurrence in dogs with a breed disposition and thus, high likelihood of routine “background noise” being reported in spontaneous AEs
  - Globally, the majority of cases are being reported by animal owner (87%) not trained in diagnosing neurologic conditions; misinterpretation of clinical signs cannot be ruled out
- Toxicokinetic profile of the active ingredient:
  - Limited systemic exposure to the actives is not toxicologically relevant
  - In the review of our PV data, chewing and/or ingestion of collar is generally related to gastrointestinal signs and not related to serious neurological signs
- Target animal safety studies:
  - Application of 5x overdose of product in VICH TAS studies did not cause convulsions/epilepsy in clinical trials, not even in physiologically immature, pediatric animals (puppies and kittens)



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# Summary

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## SUMMARY

Following Elanco's review of US-specific as well as global Seresto reports:

The safety profile of the product is stable and the benefit-risk balance is considered positive. There are no confirmed signals suggesting an unreasonable risk for exposed animals or humans. Thus, no actions are considered necessary other than continued routine signal management activities.



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# Questions / Discussion

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